Roche

Pharmaceuticals

July 6, 1999

7602 '99 JUL 12 A9:18

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 99D-0674 - Draft Guidance for Industry: IND's for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format

Dear Sir or Madam:

Hoffmann-La Roche hereby encloses its' comments to the Draft Guidance for Industry: "IND's for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format".

Sincerely,

HOFFMANN-LA ROCHE INC.

David Ridge for

Kathleen Schostack, Ph.D.
Director, Technical Regulatory Affairs
Drug Regulatory Affairs

KS:bb
Attachment
HLR No. 1999-1624

99D-0674

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Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Hoffmann-La Roche Inc.

Comments on FDA Draft Guidance for Industry
IND's for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products;
Chemistry, Manufacturing, and Controls Content and Format

July 6, 1999
Docket No. 99D-0674

General Comments:

No mention is made of electronic filing of IND information.

The requirements in the Phase 3 / Pivotal Study section specify more detail than is necessary in the IND from a safety perspective. Alternatively, provision should be made that these additional data and protocols may be filed to the IND as part of the information package submitted for an end-of-Phase 2 or pre-NDA meeting.

Specific Comments
NOTE: Added text is written in *italics*.

Section	Page	Line	Change	Comment
II. B.	2 - 3	81 - 83	The information specified in the Phase 3 / Pivotal Study section can be submitted as *part of the information package for a pre-NDA/BLA meeting* ~~summary annual reports~~ if the changes do not affect safety.	The additional information described in the Phase 3 / Pivotal Study section which is not safety related concerns drug development issues. As such, this information is best communicated via a mechanism where FDA review and guidance are sought.
III. A. 3.	4	130 - 131	The structure of the starting materials ~~and information to support the classification of a compound as a starting material~~ should be provided …	The supporting information for classification of starting materials is not needed prior to NDA.
III. A. 3.	4	152	… *unique or critical* equipment …	Specific equipment should not need to be identified unless it is unique or critical to the synthetic process.

Section	Page	Line	Change	Comment
III. A. 5.	5	190 - 192	A complete description of the *non-USP* analytical procedure and *appropriate* supporting validation data should be available on request.	Insert *non-USP* for consistency with lines 401 and 508. Insert *appropriate* for clarification since typically methods are not yet finalized at this stage in development and, therefore, complete analytical validation data are not available.
III. B. 5.	7	280 - 282	The complete description of the *non-USP* analytical procedure and *appropriate* supporting validation data should be available on request.	Insert *non-USP* for consistency with lines 401 and 508. Insert *appropriate* for clarification since complete analytical validation data are typically not available at this stage in development.
III. B. 5.	7	286 - 287	A summary table of the test results, ~~analytical data (e.g., chromatogram), and~~ *or* COA …	A tabulation of the data or COAs should be sufficient to demonstrate quality of the clinical lots.
IV. A. 1.	8	324 - 325		In addition to the requirements for characterization data concerning crystal morphology, information should be provided regarding control of the crystalline form (perhaps in Section IV. A. 3).
IV. A. 3.	9	359	… *unique or critical* equipment …	Specific equipment should not need to be identified unless it is unique or critical to the synthetic process.
IV. A. 5.	9	401	…non-USP analytical procedures ~~with~~ *should be submitted and* appropriate validation information should be ~~provided~~ *available upon request.*	Although the test methods are generally established, method validation is completed while Phase 3 is ongoing.
IV. A. 5.	10	408 - 409	Suitable limits based on ~~manufacturing experience~~ *safety* should be established.	Manufacturing experience is generally limited in nature through Phase 3. Safety should remain the basis for setting specification limits.
IV. A. 5.	10	413 - 415	A summary table of updated test results, ~~analytical data (e.g., IR spectra, HPLC chromatograms, microbial limits for incoming raw materials prior to sterilization) and~~ *or* COAs for …	A tabulation of the data or COAs should be sufficient to demonstrate quality of the clinical lots.
IV. A. 7.	10	438 - 439	~~Each table should contain data from only one storage condition.~~	Table Table of Contents Page format should not be limited as defined here. We have generally tabulated data based on lot to allow review and comparison of the data for a given lot under various storage conditions.

Section	Page	Line	Change	Comment
IV. A. 7.	10	439	~~Individual data points~~ *Results* for each test should be reported.	Clarification is needed. "Individual data points" should not mean that individual values for replicate analyses are reported (e.g., individual values for duplicate sample preparations). A single result should be reported when replicates are specified by the procedure.
IV. B. 7.	12	541	Dissolution profiling in *a* physiologically relevant media*um* …	Dissolution profiling during stability studies is generally performed using the (single) medium in the proposed specifications.
IV. B. 7.	13	548	~~Each table should contain data from only one storage condition.~~	Table format should not be limited as defined here. We have generally tabulated data based on lot to allow review and comparison of the data for a given lot under various storage conditions.
IV. A. 7.	10	439	~~Individual data points~~ *Results* for each test should be reported.	Clarification is needed. "Individual data points" should not mean that individual values for replicate analyses are reported (e.g., individual values for duplicate sample preparations). A single result should be reported when replicates are specified by the procedure.
IV. B. 7.	12	541	Dissolution profiling in *a* physiologically relevant media*um* …	Dissolution profiling during stability studies is generally performed using the (single) medium in the proposed specifications.
IV. B. 7.	13	548	~~Each table should contain data from only one storage condition.~~	Table format should not be limited as defined here. We have generally tabulated data based on lot to allow review and comparison of the data for a given lot under various storage conditions.
IV. B. 7.	13	549	~~Individual data points~~ *Results* for each test should be reported.	Clarification is needed. "Individual data points" should not mean that individual values for replicate analyses are reported (e.g., individual values for duplicate sample preparations). A single result should be reported when replicates are specified by the procedure.

Section	Page	Line	Change	Comment
V.	13	566 - 567	… data demonstrating the absence of the active ingredient should be ~~provided~~ *available upon request* for phases 2 and 3.	No specific guidance is provided for stability testing of a placebo. Although this is generally performed during development to identify degradants of the excipients and to ensure that there is no interference from such degradants, these data are generally not reported except in relevant method validation reports.

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